Pain in Axial Spondyloarthritis

Insights from Immunology and Brain Imaging

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KEYWORDS

• Spondyloarthritis • Pain • Dynamic pain connectome • Neuro-immune interface

KEY POINTS

- Immune cells interact with neurons to modulate pain through either peripheral or central sensitization depending on the site of this interaction.
- The default mode network, salience network, and antinociceptive system exhibit functional connectivity, which modulates pain perception in this condition.
- Differences in pain perception in males and females have been demonstrated both in animal models as well as on neuroimaging.

INTRODUCTION

Back pain, which is worse at rest but better with exercise, of more than 3 months in duration, in individuals younger than 45 years, is typical of spondyloarthritis (SpA).[1] Other characteristic features include alternating buttock pain or pain that awakens in the second half of the night.[2] In clinical practice though, it is not uncommon for patients to present with pain that does not always fit this description, making it difficult to establish a diagnosis early in these patients. The increased use of MRI in the diagnosis of SpA has helped identify these patients earlier but also led to an understanding that these patients may also suffer with coexisting degenerative disk disease and that both of these factors could contribute to pain.[3] The Bath Ankylosing Spondylitis Index (BASDAI), which is meant to measure disease activity in SpA, does not distinguish between inflammatory and mechanical back pain.[4,5] Imaging has also highlighted the fact that patients who experience symptoms with SpA do not always show evidence

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of active inflammatory lesions on MRI, as suggested by a recent study that showed no significant differences in Spondyloarthritis Research Consortium of Canada MRI scores in patients with low or high clinical disease activity scores.[6] Patients treated with biologic agents may show a response to treatment with lesions improving on MRI but do not disappear.[7] Pain in SpA is hence complex, multifactorial, and poorly understood.

There are also sex differences in SpA with women more likely to present with higher levels of pain.[8] Some argue that the presence of coexisting fibromyalgia may play a role in response to therapy.[9] Other factors, such as depression and anxiety, as well as sleep disorders, are common in SpA[10] and may also impact the individual's response to therapy. Functional MRI studies have recently shown the complex network of areas in the brain that are responsible for perception of pain in SpA.[11] An understanding of the differences in the immune response between the sexes has also helped better understand the difference in perception of pain and response to therapy.[12]

In this review, we describe recent advances in neuroimaging of various brain networks involved in pain in SpA. We also discuss the interface between the immune system and nervous system and how this leads to differences in pain perception between the sexes.

SOURCES OF PAIN IN AXIAL SPONDYLOARTHRITIS

Typically, the onset of pain in axial SpA is usually in the low back and is caused by inflammation of the sacroiliac joints. This may be due to synovitis, osteitis, or enthesitis at the sacroiliac joints.[13] Patients complain of alternating buttock pain, which is often responsive to nonsteroidal anti-inflammatory drugs (NSAIDs). Inflammation in the spine, seen as osteitis leading to hyperintense corner lesions at vertebral corners may be responsible for pain in other parts of the spine. Apart from osteitis, enthesitis, particularly of the anterior longitudinal ligament in the spine, and spondylodiscitis may be the cause of spinal pain.[14] In addition to the spine, inflammation of the costovertebral joints may cause anterior chest wall pain with reduced chest expansion and pain on deep inspiration.

A study comparing imaging to the site of pain, established a good correlation between site of pain and sacroiliitis but not between site of pain and spinal lesions on MRI.[15]

Later in the disease, development of syndesmophytes, as well as bony bridges, may be sources of pain. Despite excessive bone deposition, these patients are at risk of osteoporosis resulting in vertebral fractures with acute-onset back pain. Degenerative spine disease such as disk disease and spinal canal stenosis, as well as facet joint arthritis may be as common in this group of patients as it is in the general population and can coexist with inflammatory changes in the same patient.[16] Rarely, neurologic complications, such as atlanto-axial dislocation[17] or cauda equina syndrome,[18] may be seen in advanced cases. Apart from the structural causes listed previously, there have been some recent reports of cold hyposensitivity, mediated by Aδ fibers and reduced proprioception, mediated by Aβ fibers, in SpA suggesting the presence of neuropathic pain in SpA.[19]

Emotional factors, such as anxiety and depression, also may play a role in pain modulation in these patients.[10] Patients with comorbid fibromyalgia often exhibit higher pain scores and report higher overall scores on their Bath indices.[20] Patients with SpA with comorbid fibromyalgia are less likely to continue their first biologic.[21] They also tend to report only a modest response to therapy in terms of patient-reported outcomes although still show a similar drop in C-reactive protein levels.

Fatigue, poor work productivity, and poor quality of life are commonly associated with comorbid fibromyalgia.[9]

PAIN PERCEPTION

Nociceptors (somatosensory neurons that are sensitive to noxious stimuli) innervate the skin, muscles, joints, and periosteum carrying impulses via either fast-conducting Aδ myelinated fibers or slow-conducting nonmyelinated C fibers.[22] Although most nociceptors are polymodal, some are modality-specific, such as C-heat nociceptors and C-mechano-cold nociceptors.[23] Joints also show mechanoreceptors that may not be sensitive to mechanical stimuli in the absence of tissue injury. However, when joints become inflamed, these silent receptors become active and mechanosensitive, and are also called mechanically insensitive afferents.[24] These mechanoreceptors have low thresholds similar to non-nociceptor mechanoreceptors, but in the presence of inflammation, there is a reduction in the action potential leading to pain sensitivity and hyperalgesia.[25]

L-glutamate is the primary neurotransmitter of nociceptors. Nociceptors are generally of 2 types, depending on the neurotransmitter released at synapse-peptidergic or non-peptidergic.[26] Neuropeptides such as either Substance P or Calcitonin gene-related peptide (CGRP) and expression of nerve growth factor (NGF) receptor tyrosine kinase A is found in peptidergic neurons. They also show presence of transient receptor potential vanilloid 1 (TRPV1) and transient receptor potential ankyrin 1 (TRPA1) channels. Non-peptidergic nociceptors express c-Ret, the receptor for glial cell line–derived neurotrophic factors, IB4 isolectin, and express purinergic P2X3 receptor.[26] Peptidergic nociceptors serve both afferent and efferent function and are hence known as sensorimotor nerves. They release Substance P and CGRP at the site of tissue injury leading to vasodilation, increased vascular permeability, and release of mediators from mast cells, also known as neurogenic inflammation.[27]

Although cartilage does not show any evidence of nerve fibers, an abundance of neuropeptide, Substance P, has been reported in periosteum, subchondral bone, bone marrow, fat pad, and joint capsule in patients with knee osteoarthritis.[28] Bone marrow edema has been shown to be a predictor of pain in temporomandibular osteoarthritis,[29] knee osteoarthritis, osteonecrosis, reflex sympathetic dystrophy, bone contusion after trauma, and stress fractures.[30] Similar bone edema is reported in both axial[31] and peripheral SpA.[32] Low threshold mechanoreceptors, mechanically sensitive nociceptors, and silent nociceptors have been shown in facet joints on neurophysiological studies.[33] Immunohistochemistry studies of cadaveric sacroiliac joints have also demonstrated the presence of neurotransmitters Substance P and CGRP.[34] Similarly, high levels of glutamate and its N-methyl D-Aspartate (NMDA) receptor, as well as Substance P, were found on immunohistochemistry in patients with patellar tendinopathy when compared with patients with tibial shaft fractures as controls.[35]

PAIN TRANSMISSION

Noxious stimuli lead to depolarization of the nociceptor leading to activation of Transient Receptor Potential channel subtypes (TRPA, TRPM, and TRPV), Sodium channel isoforms (Nav), Potassium channel subtypes (KCNK), and acid-sensing ion channels, releasing either glutamate or neuropeptides such as Substance P or CGRP and conduction of action potentials along type A and C fibers. These then communicate with second-order neurons in the dorsal horn of the spinal cord. Second-order neurons in turn decussate in the spinal cord and join the ascending fibers of the anterolateral

system projecting to the brainstem and thalamus. Third-order neurons from the thalamus project to a number of different cortical and sub-cortical areas including the somatosensory cortex encoding sensory discriminative functions; anterior cingulate cortex, amygdala, and insular cortex encoding emotional responses; as well as prefrontal cortex encoding cognitive aspects of pain. Descending pathways modulating pain involve brainstem areas such as the peri-aqueductal gray, locus ceruleus, and rostral ventro-medial medulla.[36]

THE NEUROIMMUNE INTERFACE

Pain is a protective mechanism against tissue injury. The presence of inflammation leads to injury and is associated with pain. Resolution of inflammation in turn leads to resolution of pain, suggesting a link between the immune and nervous systems. Cytokines, lipids, proteases, and growth factors released from immune cells bind to receptors on nociceptors.[25] This binding causes activation of ion channels on the nociceptors and generation of pain impulses. In mouse models, cytokines and Prostaglandin E2 (PGE2) are released by neutrophils that migrate to the site of injury.[37] Activated mast cells that are associated with nociceptors in the mucosa on electron microscopy, release interleukin (IL)-5, IL-6, tumor necrosis factor (TNF)α, IL-1β as well as histamine, 5HT and NGF.[38] Cytokines, growth factors, and lipids are also released from macrophages and monocytes migrating to the injury site.[39,40] IL-17 A and interferon (IFN)γ released by T cells bind their receptors on nerve endings inducing pain.[41] Apart from nerve endings, immune cells also interact with the body of the nociceptors within the dorsal root ganglion with increased numbers of these cells in the dorsal root ganglion (DRG) after chemotherapy[42] and after sciatic nerve ligation induced pain[41] in animal models.

Cytokines may also activate nociceptors directly (**Table 1**).[25] p38 Membrane Associated Protein Kinase (MAPK) phosphorylation of Nav 1.8 sodium channels by IL-1β, leads to thermal hyperalgesia.[43] It can also lead to increased TRPV1 expression by activation of IL-1R on nociceptors and hence increases pain sensitivity to thermal stimuli. IL-6 binds gp-130 leading to increased expression of both TRPV1 and TRPA1.[44,45] Prostaglandins induced as a result, activate Prostaglandin EP1-EP4 receptors leading to sensitization of nociceptors to pain. Similarly, TNFα causes increased expression of TRPV1 and TRPA1 by p38 MAPK phosphorylation of Nav 1.8 and Nav 1.9 sodium channels leading to neuronal production of prostaglandins and hyperalgesia.[46–48] IL-6 induces mechanical hyperalgesia and IL-1β induces thermal hyperalgesia but TNFα induces both mechanical and thermal hyperalgesia.[49] A fast increase in neuronal excitability has been shown to be induced by IL-17A. This hypernociceptive effect has been shown to be blocked in antigen-induced arthritis mouse models by either pharmacologic or genetic inhibition of TNFα, IL-1β, CXCL1, endothelin-1, and prostaglandins.[50]

Nociceptors express chemokine receptors such as CC chemokine receptor 1 (CCR1) and CXC chemokine receptor 5 (CXCR5).[51] They also express receptors for prostaglandins and leukotrienes as well as for histamine. NGF, produced by immune cells during inflammation, can increase nerve density of the inflamed area and increase sensitivity to pain. It also produces increased oxidized lipid TRPV1 agonists and TRPV1 activity leading to persistent nociception.[52]

Nociceptors also exhibit pattern recognition receptors (PRRs) that recognize pathogen-associated molecular patterns and damage-associated molecular patterns. These PRRs include Toll-Like Receptors (TLRs) 2, 4, and 5 expressed on the cell surface, and TLRs 3, 7, and 9 expressed on endosomes, lysosomes, and the

Table 1
Sensitization of nociceptors by cytokines secreted by immune cells

Immune Cell	Cytokine Released	Receptor on Nerve Terminal	Channel Activated
Mast cells	IL-5	IL-5R	
	5-HT	5-HT2	
	Histamine	H1/2	
	NGF	TrkA	Nav1.7 & TRPV1
Mast cells, neutrophils, and macrophages	TNF α	TNF R1	Nav 1.8 & 1.9
	IL-1β	IL-1R	TRPV1
	LTB4	BLT1	
	IL-6	gp130	TRPV1 &TRPA1
Neutrophils and macrophages	PGE2	EP1-4	
Th 17 T cells	IL-17A	IL-17AR	

Immune cells, their mediators, and corresponding receptors on neurons responsible for peripheral sensitization. Inflammation leads to macrophages, monocytes, neutrophils, mast cells, as well as T cells accumulating at sites of inflammation. These cells release various mediators, including cytokines, growth factors, and prostaglandins, which in turn act on their respective receptors on neurons activating sodium channel isoforms (Nav) as well as Transient Receptor Potential cation channel subfamily vanilloid member 1 (TRPV1) and Transient Receptor Potential cation channel subfamily ankyrin member 1 (TRPA1). This leads to the depolarization of the neurons and increased sensitivity to noxious stimuli leading to hyperalgesia. Tumor necrosis factor (TNFα) binds to TNF α receptor 1 (TNFR1); interleukin (IL)-1b, which binds to IL-1 receptor (IL-1R); IL-6, which binds to gp130; prostaglandin (PG)E2, which binds to its receptor EP1-4; and leukotriene B4, which binds its receptor BLT1. In addition, mast cells secrete IL-5, which binds to IL-5 receptor (IL-5R); 5-HT, which binds to 5HT2 receptor; histamine and nerve growth factor (NGF), which bind to histamine receptor 2 (HR2) and tyrosine kinase A (TrkA) on the neuron, respectively. A subset of T cells, Th17 cells, also secrete IL-17A, which binds to IL-17A receptor (IL-17AR).

endoplasmic reticulum.[53] Cells within the nervous system such as microglia, astrocytes, oligodendrocytes, Schwann cells, satellite glial cells, fibroblasts, endothelial cells, macrophages, and sensory neurons have been shown to express TLRs. Cytokines and other soluble mediators that act on glial cells and neurons, induced by binding of TLR to its ligand, produces nociceptive hypersensitivity. ATP, which is detected by P2 purinergeic receptors, is a potent danger signal released following cell injury. Inotropic (P2X) receptors are ligand gated while metabotropic (P2Y) receptors are G-Protein coupled.[54] P2X receptors in neurons and microglia become permeable to ions leading to their activation. Sensitization of TRP and voltage-gated sodium channels in P2Y receptors contributes to nociceptor activation.

CENTRAL SENSITIZATION

Apart from nociceptors, potentiation of neurons in supraspinal areas like brainstem, thalamus, and cortex also leads to chronic pain. Activation of the immune system leads to disruption of the balance between excitatory and inhibitory processes.[55] Although this type of sensitization can be seen with nerve injury and inflammation, it also occurs in dysfunctional pain such as in fibromyalgia. These chronic pain states are associated with expansion of the receptive field such that there is an increased response to stimuli even on remote noninflamed normal tissues.[56]

Microglia have been shown to play a role in nociception.[57] Colony Stimulating Factor 1 (CSF1) released from afferent nerve fibers binds CSF1 receptor on microglia[58] inducing upregulation of ATP-sensitive P2X4 receptors on microglia in the spine.[59]

This in turn leads to activation of p38 MAP Kinase and secretion of signaling molecule Brain Derived Neurotrophic Factor (BDNF) at the synapse.[60] BDNF binds to tropomyosin receptor kinase (TRBK) on neurons in the dorsal horn of the spinal cord. This leads to downregulation of potassium-chloride cotransporter 2 (KCC2) and the phosphorylation of N-methyl-D-aspartate receptor (NMDAR) on neurons in the spinal cord transmitting signals to the brain.[61] This is required for the potentiation of NMDAR signaling. The resultant decreased inhibition and enhanced neuronal excitability results in neuropathic pain (**Fig. 1**A). The preceding process of expression of BDNF that results in sensitization of postsynaptic neurons by microglial cells has been shown in male mice. The same process is mediated by T cells infiltrating the spinal cord in female mice.[62]

Another mechanism of central sensitization is via TLR4-mediated release of inflammatory cytokines from microglia and astrocytes after chemotherapeutic cisplatin,[63] intraplantar formalin,[64] or intrathecal lipopolysaccharide (LPS) administration in mice models.[65] Activated TLR4 localizes to lipid rafts, the integrity of which is essential for TLR4 dimerization before initiation of the signaling cascade.[66–68] Removal of cholesterol from lipid rafts by Apolipoprotein A-I binding protein (AIBP) hence inhibits TLR4 signaling, which in turn reverses or prevents allodynia induced in mouse models.[69] Spinal delivery of AIBP in mouse models has been shown to significantly reduce levels of IL-6, IL-8, CCL2, and CXCL2 induced by intrathecal LPS as well as glial fibrillary acidic protein (GFAP) and ionized calcium binding adaptor molecule 1 (IBA1), markers of astrocyte and microglial activation suggesting that AIBP inhibits microglial activation in the spinal cord and may have therapeutic potential (**Fig. 1**B).[69]

Other glial cells, such as astrocytes and oligodendrocytes, also secrete inflammatory mediators like CX3CL1. This activates production of TNFα in a MAPK-dependent manner, leading to activation of spinal cord astrocytes. This in turn produces CCL2 in a JNK MAPK-dependent mechanism. CCL2 activates central neurons through CCR2 resulting in neuropathic pain.[70] Spinal cord oligodendrocytes produce IL-33, which activates microglia and astrocytes in mice hence contributing to chronic pain.[71]

SEXUAL DIFFERENCES IN CHRONIC PAIN

Mouse models show differences between male and female mice when subjected to intrathecal LPS.[72] LPS activates TLR4 in the spinal cord to induce mechanical allodynia only in male mice, but when LPS was administered in the brain or the hind paw, there was no difference between the sexes. Given that TLR4 is expressed on microglial cells, a further study showed that the microglial cells were only involved in inducing mechanical allodynia in male mice, while in female mice, adaptive immune cells such as T cells mediated the same function.[62] TAK 242, a TLR4 antagonist, was found in vitro to be effective in blocking the release of TNF from macrophages of both male and female C57Bl/6 mice treated with intrathecal LPS.[64] In the same study, intrathecal LPS-induced tactile allodynia to a greater extent in male mice, and deficiency of TLR4 as well as treatment with TAK242 reduced the allodynia more in males than females. The effect of TAK242 on preventing delayed tactile allodynia, studied by injecting intraplantar formalin, however, was the same in both males and females.

Another molecule that binds TLR4 is Spinal high mobility group box 1 protein (HMGB1), a non-histone nuclear protein, that plays an important role in both inflammation and pain processing.[73] It is reported to have a pronociceptive role in the spinal cord, DRG, and local peripheral tissues in experimental pain models of rheumatoid

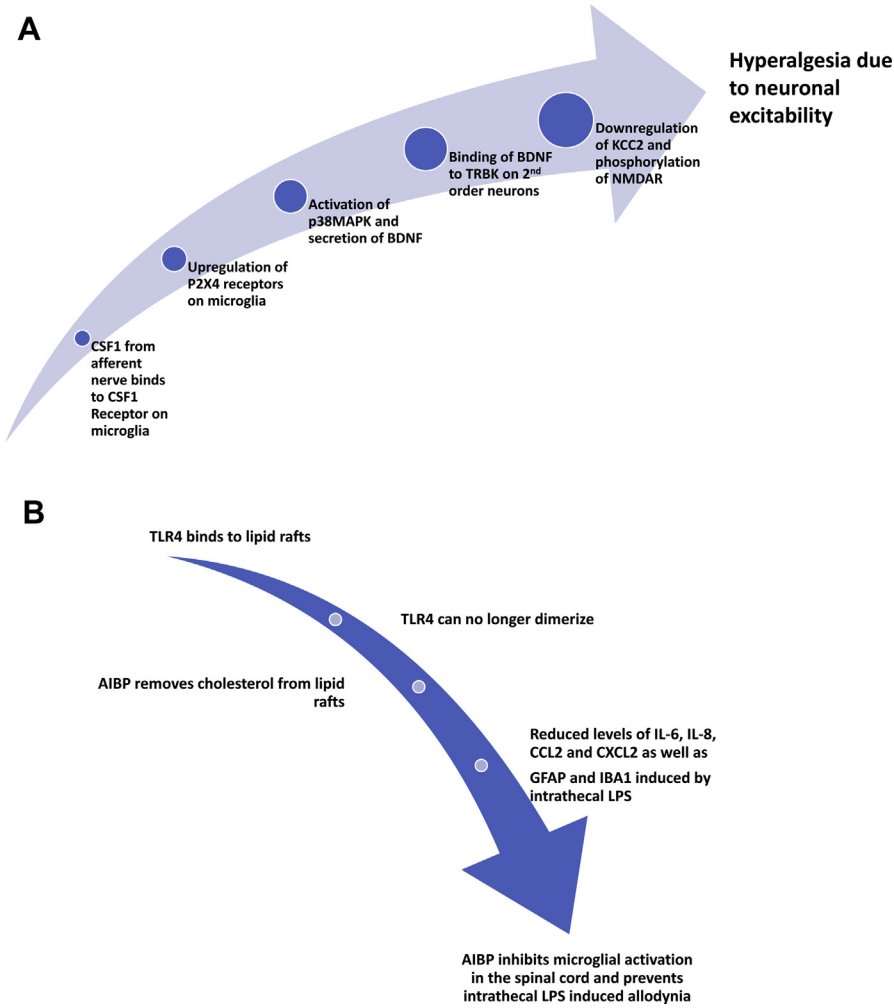

Fig. 1. Central sensitization through activation of microglia by CSF1. (*A*) Role of microglia in central sensitization of second-order neurons leading to hyperalgesia. In animal models, nerve injury results in the release of CSF1 from afferent nerve fibers, which binds CSF1 receptor on microglia. This in turn induces upregulation of ATP-sensitive P2X4 receptors on microglia in the spine leading to the activation of p38 MAP kinase and secretion of the signaling molecule BDNF, at the synapse. BDNF binds to tropomyosin receptor kinase (TRK) on neurons in the dorsal horn of the spinal cord causing downregulation of KCC2 and the phosphorylation of NMDAR on neurons in the spinal cord, thereby transmitting signals to the brain. Downregulation of KCC2 is required for the potentiation of NMDAR signaling. The resulting decreased inhibition and enhanced neuronal excitability result in neuropathic pain. The preceding process of expression of BDNF, which results in sensitization of postsynaptic neurons, has been shown to be mediated by T cells infiltrating the spinal cord in female mice, in contrast to the same process being mediated by microglial cells in male mice. Inhibition of central sensitization by AIBP through reduced microglial activation. (*B*) Another mechanism of central sensitization is via TLR4-mediated release of inflammatory cytokines from microglia and astrocytes after chemotherapeutic cisplatin, intra-plantar formalin or intrathecal LPS administration in mice models. Activated TLR4 localizes to lipid rafts, the integrity of which is essential for TLR4 dimerization prior to initiation of the

arthritis (RA).[74] The disulfide form of HMGB1, formed during inflammation, acts on TLR4 and induces cytokine production in both male and female mice.[75] However, the disulfide form of HMGB1 when injected into ankles, showed a delayed, yet longer lasting increase in mRNA of TNFα, IL1-β, IL-6, and CCL2 without inducing cellular infiltration in the ankle joints, suggesting it worked on tissue resident cells.[76] Inhibition of resident macrophages by Minocycline, reduced HMGB1-induced pain-like behavior only in male mice. Although TLR4 on nociceptors are important for HMGB1-induced pain in both sexes, the contribution of TLR4 on myeloid cells to nociception was minimal in females compared with males.[76]

In humans, 2 double-blind placebo-controlled studies from the same center showed LPS-induced systemic inflammation increases pain sensitivity was more pronounced in women as compared with men.[77] Although it is postulated that this may be sex-hormone related, no conclusive evidence of this association has been found. A study from our center of patients with ankylosing spondylitis (AS) showed sexual dimorphism with increased activation of Th17 axis in males but not females.[12] Further work is needed to understand if this difference plays a part response to therapy with IL-17 blockers.

From a clinical perspective, women show lower pain thresholds and greater temporal summation to brief repetitive stimuli than men.[78] However, they show greater adaptation to sustained noxious suprathreshold stimuli or habituation to longer sustained stimuli. Further work is needed to better understand the difference in pain perception between the sexes. Some insight into differences have become apparent from brain imaging. as discussed in the next section.

BRAIN IMAGING IN CHRONIC PAIN

Over the past decade, advances in structural and functional brain imaging have led to a better understanding of chronic pain. Depending on whether scanning involves a task, functional MRI (fMRI) scans are either stimulus or task evoked or resting state (task free).

An increase in blood flow related to increased neural activity can be detected on fMRI as Blood Oxygen Level Dependent signal, a measure of difference in magnetic properties between oxygenated and deoxygenated hemoglobin.[79] Although resting state or task-free fMRIs identify ultra-low frequency functional connectivity between brain regions, stimulus-evoked fMRI scans demonstrate how the brain reacts to noxious or non-noxious stimuli in chronic pain states. Another fMRI technique uses arterial spin labeling to monitor regional cerebral blood flow, which helps understand brain activity in a focal area related to ongoing spontaneous pain as seen in most chronic pain states.[80]

Structural MRI scans use techniques such as Voxel-based morphometry and cortical thickness analysis to quantify gray matter. Diffusion tensor imaging or tractography is another useful MRI technique to study white matter connectivity, using the difference in magnetic properties of tissues in which diffusion of water is either restricted

signaling cascade. Removal of cholesterol from lipid rafts by AIBP, hence inhibits TLR4 signaling, which in turn reverses or prevents allodynia induced in mouse models. Spinal delivery of AIBP in mouse models has been shown to significantly reduce levels of IL-6, IL-8, CCL2 and CXCL2 induced by intrathecal LPS as well as GFAP and IBA1, markers of astrocyte and microglial activation suggesting that AIBP inhibits microglial activation in the spinal cord and may have therapeutic potential.

or unrestricted. This measures fractional anisotropy on a scale between 0 and 1, where 0 represents unrestricted diffusion and 1 represents complete anisotropic diffusion.[80]

In chronic pain, the brainstem, insula, the primary and secondary somatosensory cortex, anterior and mid-cingulate cortex as well as the prefrontal cortex show altered stimulus-evoked and task-evoked responses on fMRI.[80] Abnormalities are also noted in the response and connectivity of the default mode network, salience network, and sensorimotor network. The anterior insula, medial cingulate cortex, temporoparietal junction, and dorsolateral prefrontal cortex together form the salience network. This network is more strongly activated by a noxious stimulus when the subject is paying attention to the painful stimulus. The posterior cingulate cortex, medial prefrontal cortex, lateral parietal, and area in the medial temporal lobe together form the default mode network (DMN). This network is active at rest or when attention is diverted but is suppressed when the subject is paying attention to painful stimulus. On the other hand, the antinociceptive system or the descending pain modulatory system that connects the medial prefrontal cortex of DMN and periaqueductal gray in the brainstem, shows more connectivity when the subject's attention is diverted. Individual differences in perception to pain may be accounted for by this system with those exhibiting low intrinsic attention to pain showing higher connectivity between the DMN and periaqueductal gray and others exhibiting high intrinsic attention to pain showing poorer connectivity. The dynamic nature of connectivity between the various brain regions altered with chronic pain had led to the coining of the term dynamic pain connectome (**Fig. 2**).[81]

Structural changes such as thinning of the medial cingulate cortex and anterior insula in irritable bowel syndrome[82] or thalamic gray matter volume changes in

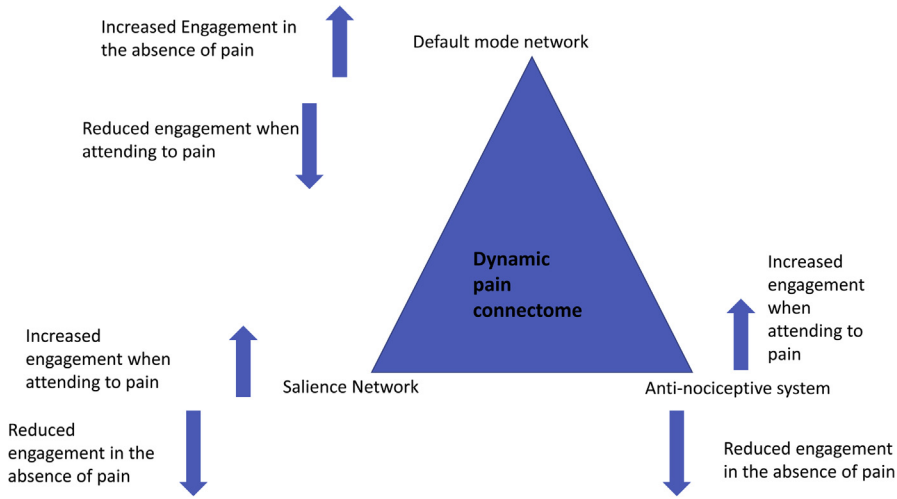

Fig. 2. Brain networks involved in pain perception. In the absence of pain, the DMN is found to be more engaged, observed on imaging. However, when exposed to a noxious stimulus, the SN and antinociceptive network show increased engagement, whereas the DMN shows reduced engagement. When attention is diverted away from pain, increased engagement of the DMN is again seen with increased functional connectivity between the prefrontal cortex of the DMN and the periaqueductal gray of the antinociceptive system.

temporomandibular joint dysfunction have also been reported.[83] These changes correlate to the duration of pain in these patients. Similar reversal of changes has also been shown in patients with chronic low back pain,[84] as well as patients undergoing hip replacement for osteoarthritis of the hips where pain resolved postoperatively.[85]

Hemodynamic-based fMRI has a temporal resolution of seconds and hence does not pick up faster occurring brain activity.[86] However, electroencephalography (EEG) or magnetoencephalography (MEG) detects abnormalities in the temporal resolution of milliseconds. These techniques show slower resting peak alpha frequency (PAF) in healthy individuals indicates greater pain sensitivity during pain.[87] Intensity of ongoing chronic pain has been related to beta and gamma power.[88] PAF slowing along with increase alpha and theta power oscillations seen in chronic pain states have been shown to reverse with treatment.[89,90] Other abnormalities include reduced beta[91] and increased gamma activity.[92] It is not clear if these changes are seen in all chronic pain states. A study of MEG in multiple sclerosis showed differences in patients with non-neuropathic pain versus those with mixed neuropathic pain.[91]

BRAIN IMAGING IN ANKYLOSING SPONDYLITIS

Cortical gray matter thinning of the primary somatosensory cortex, insular, anterior cingulate and mid-cingulate cortex, prefrontal cortex and supplemental motor area has been shown in a study of patients with AS not on biologic therapy when compared to healthy controls. It also showed increased gray matter volume of the thalamus and putamen. Decreased engagement of the somatosensory cortex and increased engagement of the anterior cingulate cortex correlated with PainDETECT questionnaire scores. All of these findings suggest a mixed picture of pain with neuropathic component of the pain in AS.[19]

A more recent study[93] measured resting-state magnetoencephalography (MEG) spectral density in 45 patients with AS versus 38 age and sex-matched healthy controls. Using PainDETECT, patients with AS were classified as non-neuropathic pain (NNP) and those that had a component of neuropathic pain (NP) in addition to inflammatory back pain. Spectral power was examined in the ascending nociceptive pathway (ANP), DMN, and salience network (SN). Patients with AS compared with healthy controls, showed an increased theta power in the DMN and decreased low-gamma power in the DMN and ANP. However, beta band attenuation or peak alpha slowing was not seen. Patients with NP had increased alpha power in the ANP when compared with healthy controls or patients with NNP. But increased alpha power within ANP was seen in those with reduced BASDAI in the NNP group and increased pain in the mixed-NP group. Thus, high alpha band activity may be a feature of NP while high theta and low gamma activity may be markers of chronic pain.[93]

Fatigue is another common manifestation of active disease in SpA that results in poor concentration and difficulty carrying out tasks due to attention deficit. The attention system consists of 3 distinct networks: the alerting network, the orienting network, and the executive control network. A study comparing 20 patients with AS with 20 age and sex-matched controls subjected to 3T MRI scans and clinical assessment for fatigue, found that fatigue scores negatively correlated to gray matter in the dorsal and ventral attention networks, the somatosensory cortex, and the caudate nucleus.[94] However, they positively correlated to gray matter in the executive control network and putamen. Decreased integrity of the white matter tracts connecting these areas as evidenced by low fractional anisotropy was also seen.

Treatment with TNF not only controls inflammation but also improves pain and fatigue; however, 3T MRI scanning in patients with AS treated with TNF inhibitors show differential effects of TNF inhibitors on pain and fatigue. Although improvement in pain with treatment has been shown to be associated with thinning of the secondary somatosensory cortex as well as motor areas, improvement in fatigue has been shown to be associated with thinning of the insula, primary somatosensory cortex, and superior temporal polysensory areas.[95]

A resting-state fMRI study of 20 patients with AS with chronic pain naïve to anti-TNF therapy versus 20 healthy controls, showed less anti-correlated functional connectivity between the SN and the DMN.[11] The degree of cross-network abnormality correlated with pain as well as disease activity. The posterior cingulate cortex was strongly connected with the SN and weakly connected to the DMN in patients versus healthy controls suggesting that the posterior cingulate cortex may be the hub for altered network interaction.

There has been a growing interest in differences between male and female individuals in terms of pain perception. A recent study that used graph theory with modular analysis and machine learning of resting-state (RS)-fMRI data in 65 patients with AS (45 male and 20 female individuals) versus 155 healthy controls, found sex-specific network topological characteristics in healthy people and those with chronic pain.[96] Higher cross-network connectivity was a feature of those with chronic pain. Higher functional segregation in the mid and subgenual cingulate cortex and lower connectivity in the network with the default mode and fronto-parietal modules was found in female individuals, whereas stronger connectivity with the sensorimotor module was exhibited in male individuals.

PHARMACOTHERAPY OF PAIN IN SPONDYLOARTHRITIS

The medical treatment of SpA usually involves a trial with NSAIDs or Cox-2 inhibitors before considering biologic agents. NSAIDs inhibit cyclooxygenase, which is required for production of prostaglandins, prostacyclins, and thromboxanes. Inhibition of PGE2 that acts on proximal ion channels to sensitize nociceptors, leads to analgesia.[97] Biologic therapy involves blocking important cytokines involved in disease pathogenesis including TNFα, IL-17, and IL-23, resulting in potent immunosuppression. fMRI studies in patients with RA on TNF blockers have been additionally shown to block nociceptive pathways in the thalamus, somatosensory cortex, as well as the limbic system within 24 hours of administration.[98]

Despite all these therapies, there remain 20% to 30% of patients that fail to respond to treatment. Simple analgesics such as acetaminophen or opiate derivatives are not very effective in management of pain in these conditions.[99] With the use of cannabis being legalized around the world, there is a growing interest in this being a potential addition to the list of medications used in this condition. Although self-usage of cannabinoids is reported to be high,[100] evidence of response from randomized clinical trials to prove its efficacy in arthritis is awaited. Given our new understanding of neuropathic nature of pain in some patients with SpA, whether neuropathic medication will prove to be effective in this condition remains to be seen.

SUMMARY

There has been a significant advance in our understanding of pain mechanisms in SpA both through animal models as well as newer modes of neuroimaging. Structural and fMRI show differences in different pain states as well as individuals and newer ways of imaging continue to evolve that may further enhance our understanding of pain. It is

now clear that rather than single brain regions, connectivity of different brain networks plays an important role in pain perception and modulation. Important differences between the sexes have been noted both on neuroimaging as well as in animal models that suggest that male and female individuals process pain differently. Although inflammation is an important cause of pain in SpA, evidence now suggests that there may be a neuropathic component of pain in this condition that may need to be addressed in a subgroup of patients.

CLINICS CARE POINTS

- Pain in SpA is multifactorial and includes inflammatory, degenerative, and in some cases neuropathic components.
- The neuroimmune interface allows for a number of immune cells, cytokines, and chemokines to interact with nociceptors as well as cells such as microglia in the nervous system resulting in both peripheral and central sensitization.
- Advances in neuroimaging have illustrated the dynamic nature of connectivity between various brain networks in pain conditions.
- Important differences exist between the sexes in pain pathways, which may have an impact on treatment.

DISCLOSURE

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